CENTER FOR DRUG EVALUATION AND RESEARCH

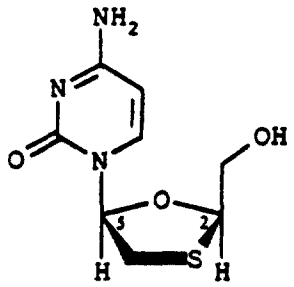
Application Number 21-003
21-004

PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

REVIEWER		: Prabhu Rajagopalan, Ph. D.
NDA (FORMULATION)		: 21003 (Tablet) and 21004 (Solution)
TYPE		: 1P
APPLICANT		: GlaxoWellcome
DRUG (ROUTE OF ADMINISTRATION)		: Lamivudine (oral)
STRENGTH	Tablet	: 100 mg
	Solution	: 5 mg/ml
SUBMISSION DATE		: June 24, 1998 and June 30 , 1998.
DRAFT REVIEW		: September 21, 1998
FINAL REVIEW		: November 16, 1998

BACKGROUND



Lamivudine ((-)2',3'-dideoxy, 3'-thiacytidine) is a nucleoside analog which has been approved for the treatment of HIV infection. Intracellularly, lamivudine is phosphorylated to lamivudine triphosphate and it is believed that incorporation of lamivudine triphosphate into the viral DNA results in chain termination. The Applicant proposes to market lamivudine under the trade name EPIVIR-HBV.

The Applicant has evaluated the safety and efficacy of lamivudine in the treatment of chronic hepatitis B infection in four Phase III studies. In Study NUCA3010, the Applicant compared the safety and efficacy of lamivudine administered at a dose of 100 mg QD for 52 weeks to that of placebo. In another 52-week study, NUCB3009, the safety and efficacy of 25 mg and 100 mg QD of lamivudine was compared to that of placebo. In the third study, NUCB3010, three regimens were examined. Patients were randomly assigned to receive lamivudine 100 mg once daily for 52 weeks (Arm 1) or lamivudine 100 mg QD for 8 weeks followed by lamivudine 100 mg QD and interferon-α 10 MU subcutaneously three times a week for 16 weeks (Arm 2). Arm 3 was identical to Arm 2 except that patients received placebo instead of lamivudine. These three studies were conducted in treatment naïve patients.

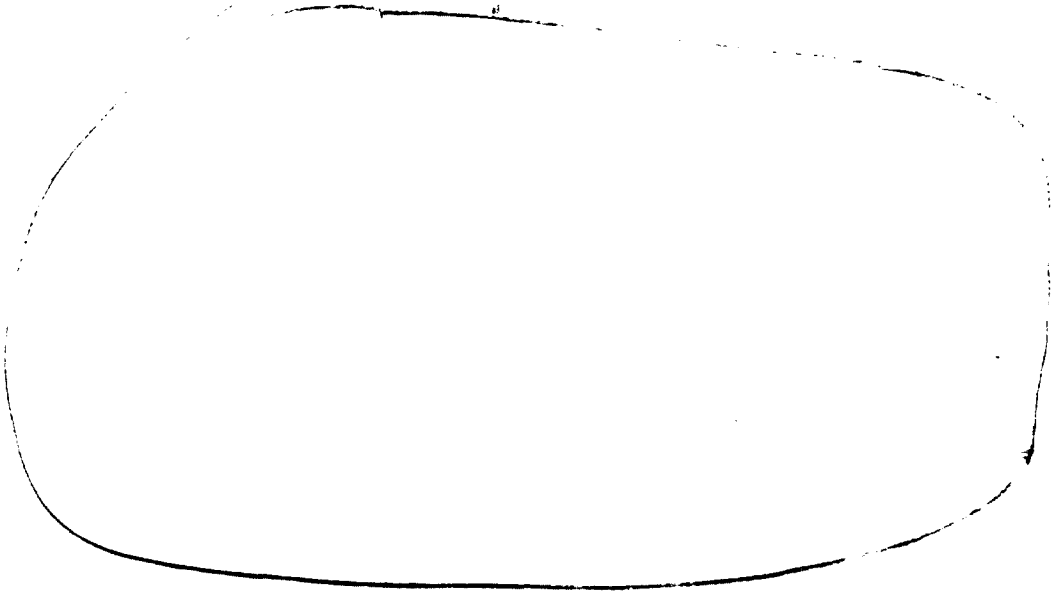
The fourth study, NUCAB3011, was conducted in interferon non-responders. Patients received lamivudine 100 mg QD or placebo for 52 weeks in Arms 1 and 2, respectively. In Arm 3, patients received lamivudine 100 mg QD for 8 weeks followed by lamivudine 100 mg QD and interferon-α 10 MU subcutaneously three times a week for 16 weeks. Approval is being sought for tablet and solution formulations of lamivudine. The recommended dose of lamivudine is 100 mg once daily.

SYNOPSIS

The important features in the pharmacokinetics and disposition of lamivudine are presented in the synopsis. A detailed review begins on page 6. Unless specified otherwise, in all subsequent sections, the variation in the mean is represented by the standard deviation associated with the mean and is shown as mean ± SD.

ABSORPTION

Following oral administration, lamivudine was absorbed with a t_{max} value that was usually less than 1.5 hours. In 16 male subjects receiving the proposed market tablet



DOSE PROPORTIONALITY

After oral administration of lamivudine to HBV infected patients, limited data indicate dose proportional increases in C_{max} and AUC values in the range 5 to 600 mg.

ABSOLUTE BIOAVAILABILITY

The absolute bioavailability of lamivudine (EPIVIR®) was assessed in 12 adult HIV infected patients. The mean absolute bioavailability was estimated to be 86% ± 16% (see EPIVIR® label).

BIOEQUIVALENCY

The Applicant conducted two bioequivalency studies to 'link' formulations of lamivudine that have been used in clinical trials. In the first study (NUCB1005), the Applicant compared lamivudine capsules (25 mg and 100 mg) to lamivudine tablets (25 and 100 mg). The capsule formulation was used in Phase 2 studies and tablet formulation was used in Phase 3 studies. The results of statistical analyses are summarized below.

Strength	PK parameter	Formulation	Point estimate	90% CI
25 mg	C_{max}	Capsule	100	
		RT2 tablet	93	[82 – 106]
	AUC_∞	Capsule	100	
		RT2 tablet	93	[87 – 99]
100 mg	C_{max}	Capsule	100	
		RT2 tablet	113	[99 – 128]
	AUC_∞	Capsule	100	
		RT2 tablet	107	[101 – 114]

In Study NUCB1006, the Applicant compared RT2 tablet to MRT4 tablet and MRT4 tablet to MRT4 solution. The MRT4 tablet and solution are the proposed market formulations. The results of statistical analyses are summarized below.

Strength	PK parameter	Formulation	Point estimate	90% CI
100 mg	C_{max}	RT2 tablet	100	
		MRT4 tablet	95	[83 – 110]
	AUC_∞	RT2 tablet	100	
		MRT4 tablet	97	[91 – 104]
100 mg	C_{max}	MRT4 tablet	100	
		MRT4 solution	123	[106 – 141]
	AUC_∞	MRT4 tablet	100	
		MRT4 solution	102	[96 – 109]

These two bioequivalency studies indicate that the exposure to lamivudine by administering the different formulations is not statistically significantly different. The C_{max} after administration of the solution formulation was significantly greater than the C_{max} observed after administration of the tablet formulation. However, this increase in C_{max} is not considered to be clinically significant.

DISTRIBUTION

The distribution of lamivudine was characterized in asymptomatic HIV infected patients. After intravenous administration of lamivudine to 20 patients, the mean apparent volume of distribution was 1.3 ± 0.4 L/kg (see EPIVIR® label). The plasma protein binding of lamivudine was less than 36%.

METABOLISM AND ELIMINATION

Metabolism of lamivudine to the trans-sulfoxide metabolite is a minor route of elimination. Lamivudine undergoes significant renal elimination. In 20 HIV-infected patients, the renal clearance of lamivudine averaged [redacted] administration. This represents approximately 70% of total clearance (see EPIVIR® label).

DRUG INTERACTIONS

A significant pharmacokinetic interaction was not observed upon concomitant administration of lamivudine (at steady state) and a single dose of interferon.

SPECIAL POPULATION

Subjects with hepatic impairment

The Applicant conducted a pharmacokinetic study in subjects with hepatic impairment. ^{14}C-aminopyrine breath test was used for classifying 16 subjects as moderately impaired (n=8) or severely impaired (n=8). Comparison of single dose pharmacokinetics of lamivudine in these subjects and healthy subjects did not reveal any significant differences in the disposition of lamivudine as a result of hepatic impairment. Therefore, a dose adjustment is not required for patients with hepatic impairment.

The Applicant also conducted a clinical trial to assess the pharmacokinetics and efficacy of lamivudine in chronic hepatitis B infected patients in end stage liver failure undergoing liver transplantation. Pre and post-transplantation AUC values in the end stage liver failure patients were approximately [redacted] greater than the AUC values observed in healthy subjects. Relatively diminished renal function in subjects with hepatic impairment could be partly responsible for the increase in AUC.

Subjects with renal impairment

A single dose pharmacokinetic study conducted by the Applicant indicates significant changes in the pharmacokinetics of lamivudine in subjects with renal impairment. The average AUC_∞ in control subjects with creatinine clearance greater than 80 mL/min was 5280 ng.h/mL. In a group of subjects with creatinine clearance in the range of 20 to 50 mL/min, the average AUC_∞ increased to 14670 ng.h/mL. In a group of subjects with severe renal impairment (creatinine clearance less than 20 mL/min), the AUC_∞ values averaged 27440 ng.h/mL. The AUC_∞ values reported above have been normalized to a dose of 100 mg and the percent coefficient of variation ranged from 19 to 26% in these groups. Based on these results, the Applicant has recommended dose adjustment for patients with varying degrees of renal dysfunction.

The Applicant also examined the effect of hemodialysis on the pharmacokinetics of lamivudine. The average between-dialysis and during-dialysis AUC_∞ values after administration of a single dose of 100 mg of lamivudine were [redacted]. Therefore, the Applicant has not recommended any additional dose modification (other than reductions based on creatinine clearance) for patients undergoing hemodialysis.

Pediatric patients

The pharmacokinetics of lamivudine were assessed in HBV infected pediatric patients in the age range, 2 – 17 years. The pharmacokinetics were determined at the following dose levels: 0.35 mg/kg BID, 1.5 mg/kg BID, 4 mg/kg BID, 3 mg/kg QD and 100 mg QD. In pediatric patients, the AUC at a dose of 1.5 mg/kg (which is approximately equal to the adult body weight normalized dose) was half the value seen in adults. The mean AUC value at a dose of 3 mg/kg was slightly higher than the exposure seen in adults. This observation is consistent with the results of previous studies indicating that the clearance of lamivudine is increased and the bioavailability is decreased in children (HIV infected). At this time, a formal dosing recommendation has not been made for pediatric patients.

Geriatric patients

The Applicant conducted a study to compare the pharmacokinetics of lamivudine in healthy elderly male subjects and healthy young male subjects. Summary data indicate that the mean AUC value in elderly subjects is ~40% greater than that observed in young subjects. This increase in exposure can be explained, in part, by reduced renal function. The mean (range) creatinine clearances in the young and elderly subjects who participated in this study were 111 mL/min (91 – 130) and 78 mL/min (70 – 91), respectively.

PK-PD CORRELATION

The Applicant conducted a dose ranging study to assess the pharmacokinetics and anti-HBV activity of lamivudine in adult patients. Placebo and various doses of lamivudine (5, 20, 100, 300 and 600 mg) were administered once daily for 4 weeks. The sigmoid E_{max} model was used to describe the relationship between exposure (AUC) and percent drop in HBV DNA. This modeling approach suggests maximum decrease in HBV DNA levels start to occur in the range of exposure that is observed following administration of 100 mg once daily. The percent of patients with HBV DNA below the limit of quantitation increased with increasing dose levels of lamivudine. At the 100 mg dose level, HBV DNA level was below the limit of detection in 67% of the patients.

DISSOLUTION METHOD

[redacted]

This dissolution method and the dissolution specification, [redacted] proposed by the Applicant are acceptable.

RECOMMENDATION

The human pharmacokinetic studies submitted under NDA 21003 and NDA 21004 provide an understanding of the pharmacokinetics of lamivudine and fulfills the requirements of Section 320 of the Code of Federal Regulations (21 CFR). Adequate pharmacokinetic information has been provided to support approval of EPIVIR-HBV™.

LABEL

The proposed label is attached to this review.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS BRIEFING

The briefing was held on September 29, 1998 and was attended by Drs. Reynolds, Lazor, Bashaw, Ajayi, Sahajwalla, Selen and Rajagopalan.

/S/ 11/17/98

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Reviewer, Pharmacokinetics
Division of Pharmaceutical Evaluation III, OCPB

Concurrence: /S/ 11-17-98

Kellie S. Reynolds, Pharm. D.
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cc:	HFD-530	/NDA 21003
		/NDA 21004
		/MO/Stryt
		/CSO/Zeccola
	HFD-880	/Rajagopalan
	HFD-880	/TL/Reynolds
✓	HFD-880	/DPE III
✓	CDR	/Barbara Murphy

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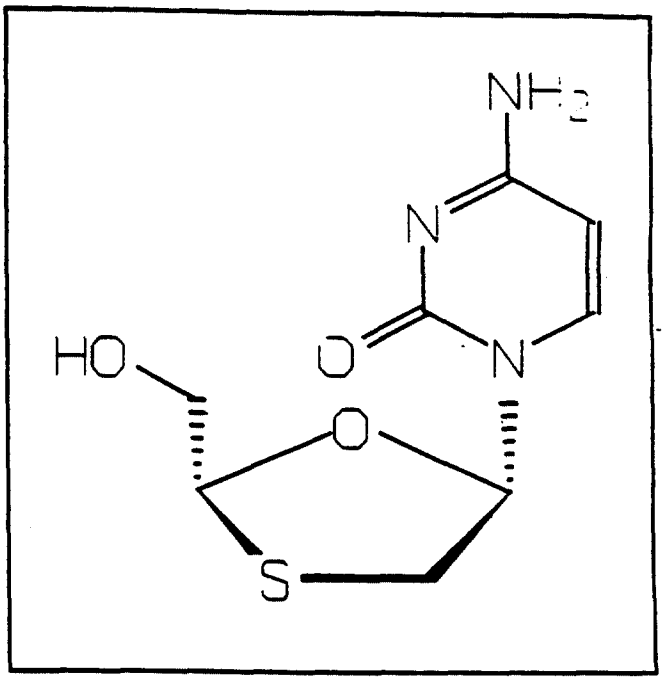
PHARMACOLOGIST'S REVIEW

NDA 21-003.000
Date Submitted: June 25, 1998
Date Assigned: June 25, 1998
Date Completed: July 6, 1998
Reviewer: Pritam S. Verma
Division: DAVDP
HFD-530



SPONSOR: Glaxo, Inc.
Research Triangle
Park, NC 27709

DRUG: Epivir®-HBV™ (lamivudine)
Tablets
Generic Name:
Lamivudine
Chemical Names:
A: (2R-cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5yl)-(1H)-pyrimidin-2-one
B: (2R-cis)-4-amino-1-[2-hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1H)-pyrimidinone
Code Name:
CAS #: 134678-17-4
Other Name: 3TC
Molecular Formula: $C_8H_{11}N_3O_3S$
Molecular Weight: 229.3
Melting Point: 177°C
pKa: 4.30 (protonation of NH_2)
Solubility: In water at 20°C about 70 mg/ml
Physical Description: White to off-white crystalline solid

DRUG CLASS: Nucleoside analog

ROUTE OF ADMINISTRATION: Oral

CLINICAL FORMULATIONS:

EPIVIR-HBV Tablets are for oral administration. Each tablet contains 100 mg of lamivudine and the inactive ingredients microcrystalline cellulose, sodium starch glycolate and magnesium stearate. Opadry YS-1-17307-A Butterscotch is the coloring agent in the tablet coating.

EPIVIR-HBV Oral Solution is for oral administration. One milliliter (1 ml) of the solution contains 5 mg of lamivudine (5 mg/ml) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben, propylene glycol, propylparaben, sodium citrate (dihydrate) and sucrose.

RELATED NDAs/

INDICATION: Treatment of Chronic Hepatitis B infection

INTRODUCTION AND DRUG HISTORY:

Lamivudine the (-) enantiomer of 4-amino-1-[2-hydroxymethyl)-1, 3-oxathiolan-5-yl]-(1H)-2-pyrimidinone is a dideoxynucleoside analog developed as a potential treatment for individuals infected with HIV and hepatitis B virus (HBV). The principle mode of action of this compound is inhibition of reverse transcription via viral DNA chain termination; that is, inhibition of the RNA- and DNA-dependent DNA polymerase activities of the reverse transcriptase by the active triphosphate form of lamivudine.

Under NDA 20-596, lamivudine 150 mg tablets and lamivudine 10 mg/ml oral solution were approved for the treatment of patients with HIV infection. Presently, The sponsor has submitted NDA 21-003 which describes the development of lamivudine 100 mg tablets and lamivudine 5 mg/ml solution for the treatment of HBV infection. The NONCLINICAL PHARMACOLOGY, PHARMACOKINETICS AND TOXICOLOGY TECHNICAL SECTIONS of the NDA have been reviewed previously in NDAs 20-564 and 20-596. Summary of the NDAs is hereby incorporated as appendix # 1. The newly submitted Pharm/Tox reports will be reviewed here as a part of the present NDA.

TOXICOLOGY:

Toxicity Studies Summary: The following studies were conducted in accordance with the FDA Good Laboratory Practices Regulations.

1. Lamivudine: oral (dietary) oncogenicity study in B6C3F1 mice (M13286), Lot # UFP005/0006/0011/1021, 1996, (WPT/95/297/GXO/528)

2. Lamivudine: oral (dietary) oncogenicity study in Han Wistar rats, Lot # UFP005/0008/0001/1026, 13 November 1996, (WPT/95/298/GXO/527/960153)

3. Lamivudine: mammalian cell mutation test at the thymidine kinase locus in mouse lymphoma L51178Y cells (T21234), Lot # UFP1027/1, 2 February 1996, (WPT/96/029)

4. Lamivudine: lack of activity in a bone marrow micronucleus test following oral administration to male Han Wistar rats, Lot # UFP1027/1, 7 June 1996, (WPT/96/028)

5. Lamivudine: supplementary report to 13-week oral toxicity study of lamivudine in dogs, Glaxo Ltd, Hertfordshire, England, 17 October 1994, (VTX/94/037)

6. Summary report of lamivudine: pericardial effusion as an artifact in the AHA rat foetus, Glaxo Ltd, Hertfordshire, England, 12 July 1995, (WPT/95/213)

Toxicity Studies Review:

1. Lamivudine: oral (dietary) oncogenicity study in B6C3F1 mice (M13286), Lot # UFP005/0006/0011/1021, 16 September 1996, (WPT/95/297/GXO/528)

Groups of male and female B6C3F1 mice (age: 6 weeks; body weights: ♂ 16-26 g and ♀ 15-22 g) received lamivudine in the diet for a period of 104 weeks according to an experimental design shown in Table 1. The mice were housed singly in a plastic cage measuring 15*33*13 cm. All animals were observed for signs of ill health or response to treatment once daily, with a second daily observation for dead or moribund animals. An examination of palpable masses was carried out at least once weekly. During week 5, 26, 52, 78 and 104, blood samples were taken at the following timepoints: 00:00, 04:00, 08:00, 16:00 and 20:00 hr. Different

mice were sampled at each timepoint. Statistical analysis were carried out separately for males and females.

Table 1
Experimental design of oral oncogenicity study in mice

Dosage Group (mg/kg/day)	Mean dose levels achieved: weeks 1-104 (mg/kg/day)		Number of mice			
			Main group		Toxicokinetic group	
	male	female	male	female	male	female
Vehicle control	0	0	60, 60	60, 60	15	15
180 (low)	182	181	60	60	30	30
600 (mid)	606	605	60	60	30	30
2000 (high)	2025	2014	60	60	30	30

Results: there was no clinical signs indicative of a reaction to treatment. The overall mortality incidence and distribution is shown in Table 2. Group mean body weight gain was lower at all dosages for males during weeks 0-35 and for females during weeks 0-104 compared with controls, the effect being dose-related in degree (Table 3). Mean absolute body weights for selected weeks are shown in Table 4. There was no effect of treatment on food intake.

Table 2
Overall mortality incidence and distribution (main group) during the 104 weeks of mice oncogenicity study

Dosage Group (mg/kg/day)	Number of mice							
	Initial group size		# of dead: week 1-104		% mortality		% survival	
	male	female	male	female	male	female	male	female
Vehicle control	120	120	20	28	17	23	83	77
180 (low)	60	60	10	17	17	28	83	72
600 (mid)	60	60	7	11	12	18	88	82
2000 (high)	60	60	6	6	10	10	90	90

Table 3
Group mean weight gains (g/mouse) during the 104 weeks in mice oncogenicity study

Dosage Group (mg/kg/day)	group mean weight gains (g/mouse)					
	weeks 0-35		weeks 35-104		weeks 0-104	
	male	female	male	female	male	female
Vehicle control	19.4	18.1	3.7	10	22.9	28.1
180 (low) % of control	16 82**	16.6 92*	4.6	7.9	20.7 90*	24.1 86**
600 (mid) % of control	13.9 72**	13.3 73**	3.4	6.5	17.1 75**	19.7 70**
2000 (high) % of control	11.4 59**	10.9 60**	3.7	4.4	15.2 66**	15.2 54**

* = p <0.05
** = p <0.01

Table 4
Group mean weights during the 104 weeks in mice oncogenicity study

Dosage Group (mg/kg/day)	group mean weights (g)					
	weeks 0		week 35		week 104	
	male	female	male	female	male	female
Vehicle control	22	18	42	37	45	47
180 (low)	22	19	39	36	43	43
600 (mid)	23	19	37	32	40	38
2000 (high)	22	19	34	30	37	34

Hematology: at all doses for both sexes, mean total WBC values were slightly lower compared with controls; dose-related and statistically significant for males. This was due mainly to lower mean lymphocyte values at all doses; statistically significant and dose-related for males. There were lower mean neutrophil values for males at all doses and females (mid and high). The mean total RBC value for females (high) was statistically significantly lower compared with controls. There were no apparent treatment-related differences for RBC morphology compared with controls. Drug absorption: mean AUC and Cmax values are shown in Table 5. Overall achieved dosages ranged from 99.7 to 101.3% of the target doses. Plasma levels increased with increasing dose. There were no significant differences in plasma levels between the sexes or with duration of treatment.

Table 5

Mean AUC values in week 5 and predicted Cmax values from oncogenicity study in mice

Dosage Group (mg/kg/day)	AUC (µg*hr/ml week 5	Cmax (µg/ml) weeks				
		5	26	52	78	104
180 (low)	16.4	1.2	1.5	<1.1	1.7	1.1
600 (mid)	47.6	3.5	4.7	3.9	5.1	3.4
2000 (high)	151	9.5	13.9	10.7	14.2	9.7

For a clinical dose of 150 mg bid, the average steady state systemic exposure (AUC) and peak plasma concentration (Cmax) values were 7.8 µg*hr/ml and 1.9 µg/ml, respectively. The average systemic AUCs measured at week 5 of the study were 16.4 (low), 47.6 (mid) and 151 (high) µg*hr/ml. Based on the average AUC and Cmax in the clinic, the high dose in the study represented 19-fold (AUC) and 5-fold (Cmax) overdosages, respectively. Macroscopic Pathology: revealed no changes considered to be attributable to treatment. Microscopic Pathology - Neoplastic Findings: there was a slight non-dose related increase in histiocytic sarcoma in female mice (Table 6, low and high). Statistically, the trend was not significant (p=0.173). There were no statistically significant results for an increasing trend in tumors rates.

Table 6

Neoplastic finding in females only during the 104-week oncogenicity study of mice

Neoplastic finding	Dosage levels (mg/kg/day)				
	Controls		low	mid	high
	0	0	180	600	2000
Histiocytic sarcoma	1	2	6	3	5
Total # of mice examined	60	60	60	60	60

Non-Neoplastic Findings in Males: are shown in Table 7. Kidney: there was a slight non-dose related increase in the incidence of trace mineralization in the cortex in male mice from all treated groups. This increased incidence was not seen in female mice and was considered to be a minor exacerbation of a normal age-related finding.

Table 7
Non-neoplastic finding in males only during the 104-week oncogenicity study of mice

Non-neoplastic finding in male		Dosage levels (mg/kg/day)				
		Controls		low	mid	high
		0	0	180	600	2000
Mineralization in the cortex	total	31	29	45**	44**	38
	trace	25	17	32**	30*	34**
	minimal	6	12	13	14	4
Total # of kidneys examined		60	60	60	60	60

* = p <0.05, ** = p <0.01, one-sided, Fischer's Exact Test, combined controls compared with low, mid and high dose groups.

Non-Neoplastic Findings in Females: are shown in Table 8. Femur/joint: there was an increased incidence of epiphyseal cancellous bone, increased bony trabeculae of diaphysis and focal remodelling of the femoral shaft in female mice (mid and high). These findings were not dose-related but were statistically significant with a Fisher's test (mid and high) for increased epiphyseal cancellus bone and focal remodelling of the femoral shaft. Other Findings: there was a statistically significant increased incidence of acinar degeneration/necrosis of the Harderian gland in male mice (high).

Table 8
Non-neoplastic findings in females only during the 104-week oncogenicity study of mice

Non-neoplastic finding in females	Dosage levels (mg/kg/day)				
	Controls		low	mid	high
	0	0	180	600	2000
Increased epiphyseal cancellous bone	4	5	10	18**	12*
Increased bony trabeculae of diaphysis	23	24	27	32	30
Focal remodelling of the femoral shaft	12	12	8	22*	26**
Total number of femurs examined	60	60	60	60	60

Fisher's Exact Test, combined controls compared with low, mid and high dose groups.

* = p <0.05
** = p <0.01, one sided

Comments: The potential oncogenicity of lamivudine was investigated in mice at dosages of 180, 600 or 2000 mg/kg/day in comparison with untreated controls for a period of 104 weeks. The study protocol was approved by the ECAC.

Histopathological examination showed a slightly higher incidence of histiocytic sarcomas in the low and high dosage female mice. There was no trend with dose and the incidences were similar to historical controls. The occurrences of histiocytic sarcoma were considered to be incidental to treatment with lamivudine.

There was a slight, but non-dose-related, increase in the incidence and degree of mineralization of the cortex of the kidney of all treated male mice. In the femur of female mice (mid and high), there was a non-dose-related increase in bone deposition. Both of these findings were considered to be exacerbations of normal age-related changes in mice.

Lamivudine was not oncogenic in mice. For oncogenic potential, a dosage of 2000 mg/kg/day was the NOEL. For a clinical dose of 150 mg bid, the average steady state systemic exposure (AUC) was 7.8 µg*hr/ml. The average systemic AUC measured at the dose level of 2000 mg/kg/day during week 5 of the study was 151 µg*hr/ml. Based on the average AUC in the clinic, the high dose in the mice study represented a 19-fold increase; thus, an equivalent dose in humans would be 2850 mg bid.

2. Lamivudine: oral (dietary) oncogenicity study in Han Wistar rats, Lot # UFP005/0008/0001/1026, , 13 November 1996, (WPT/95/298/GXO/527/960153)

Groups of male and female Han Wistar rats (strain: HanIbm; age: 6 weeks; body weights: ♂ 117-170 g and ♀ 96-141 g) received lamivudine in the diet for a period of 104 weeks according to an experimental design shown in Table 9. The rats were housed singly in a plastic cage measuring 36.5*55*25 cm. All animals were observed for signs of ill health or response to treatment once daily, with a second daily observation for dead or moribund animals. An examination of palpable masses was carried out at least once weekly. During week 5, 26, 52, 78 and 104, blood samples were taken at the following timepoints: 00:00, 04:00, 08:00, 16:00 and 20:00 hr. Different rats were sampled at each timepoint. Statistical analysis were carried out separately for males and females.

Table 9
Experimental design of oral oncogenicity study in rats

Dosage Group (mg/kg/day)	Mean dose levels achieved: weeks 1-104 (mg/kg/day)		Number of rats			
			Main group		Toxicokinetic group	
	male	female	male	female	male	female
Vehicle control	0	0	55, 55	55, 55	20	20
♂=180 (low) ♀=300 (low)	180	300	55	55	20	20
♂=600 (mid) ♀=1000 (mid)	598	1000	55	55	20	20
♂=2000 (high) ♀=3000 (high)	2002	3008	55	55	20	20

Results: there were no clinical signs indicative of a reaction to treatment. The overall mortality incidence and distribution is shown in Table 10. There was no treatment-related effect on survival at any dosage. Group mean body weight gain males, and particularly females (high) showed lower mean body weight gains compared with controls for the majority of the 104 weeks of treatment. Slightly lower mean weight gain, mainly during the first 16 weeks of treatment was evident for males (mid) and females (low or mid, Table 11). Mean absolute body weights for selected weeks are shown in Table 12. Food consumption: was slightly, but generally consistently higher from week 14 for

males (high) and from week 46 for females (high), when compared with the respective controls.

Table 10

Overall mortality incidence and distribution (main group) during the 104 weeks of the rat oncogenicity study

Dosage Group (mg/kg/day)	Number of rats							
	Initial group size		# of dead: week 1-104		% mortality		% survival	
	male	female	male	female	male	female	male	female
Vehicle control	110	110	19	30	17	27	83	73
180♂/300♀ (low)	55	55	10	19	18	35	82	65
600♂/1000♀ (mid)	55	55	8	13	15	24	85	76
2000♂/3000♀ (high)	55	55	11	13	20	24	80	76

Table 11

Group mean weight gains (g/mouse) during the 104 weeks in rat oncogenicity study

Dosage Group (mg/kg/day)	group mean weight gains (g/rat)					
	weeks 0-16		weeks 35-104		weeks 0-104	
	male	female	male	female	male	female
Vehicle control	263	118	103	106	447	255
180♂/300♀ (low) % of control	262 100	112** 95	93 90	112 106	437 99	254 100
600♂/1000♀ (mid) % of control	250* 95	111** 94	100 97	91 86	432 97	234* 92
2000♂/3000♀ (high) % of control	248** 94	108** 92	79* 77	74** 70	408** 92	209** 82

* = $p < 0.05$
** = $p < 0.01$

Table 12

Group mean body weights (g) during the 104 weeks in rat oncogenicity study

Dosage Group (mg/kg/day)	group mean weights (g)					
	week 0		week 35		week 104	
	male	female	male	female	male	female
Vehicle control	141	119	482	269	585	374
180♂/300♀ (low)	142	120	490	263	581	375
600♂/1000♀ (mid)	141	118	470	261	574	351
2000♂/3000♀ (high)	143	119	470	255	552	328

Hematology: there were no apparent effects on RBC count or WBC counts/profile. There were no apparent treatment-related differences for RBC morphology compared with controls. Drug absorption: mean AUC and Cmax values are shown in Table 13. Overall achieved dosages ranged from 99.7 to 100.3% of the target doses. Plasma levels increased with increasing dose. There were no significant differences in plasma levels with duration of treatment. Plasma levels were generally proportional to dose.

Table 13

Mean AUC values in week 5 and predicted Cmax values from oncogenicity study in rats

Dosage Group (mg/kg/day)	AUC (µg*hr/ml week 5	Cmax (µg/ml)				
		weeks				
		5	26	52	78	104
180♂/ 300♀ (low)	52♂ 98	2.7 5.5	3 4.3	3.1 4.2	4.4 7.4	3.5 5.5
600♂/ 1000♀ (mid)	172 312	9 18	10 14	8 13	17 19	13 17
2000♂/ 3000♀ (high)	533 880	28 48	27 41	21 35	40 43	28 38

For a clinical dose of 150 mg bid, the average steady state systemic exposure (AUC) and peak plasma concentration (Cmax) values were 7.8 µg*hr/ml and 1.9 µg/ml, respectively. The average systemic AUCs measured at week 5 of the study were 52♂/98♀ (low), 172♂/312♀ (mid) and 533♂/880♀ (high) µg*hr/ml. Based on the

average AUCss in the clinic, the high dose in the study represented 68- to 113-fold overdosages. Macroscopic Pathology: revealed distension of the bile duct in a greater number of males (high) compared to the controls. Microscopic Pathology - Neoplastic Findings: there was an increased incidence of endometrial epithelial tumors in female rats when compared with the controls (Table 14, high). The increase was not considered significant for a common tumor in trend test both for adenocarcinoma alone (p=0.048) and when taken together with adenoma (p=0.017). There was no increased incidence or trend for endometrial tumors in the treated rats (low or mid).

Table 14

Neoplastic findings in females only during the 104-week oncogenicity study of rats

Neoplastic finding	Dosage levels (mg/kg/day)				
	Controls		low	mid	high
	0	0	300	1000	3000
Endometrial adenocarcinoma	2	2	1	2	5
Endometrial adenoma	0	0	0	0	1
Total number of rats examined	55	55	55	55	55

Non-Neoplastic Findings in Males and Females: are shown in Tables 15 and 16. There was an increase in the incidence and severity of mineralization in male rats (high). This increase was accompanied by an increased incidence of dilated suburothelial capillaries. In female rats, there was a marginal increase in the incidence of mineralization (mid or high). No increased incidence of these changes was seen in male rats (low or mid) or female rats (low) when compared with control rats.

Table 15
Non-neoplastic findings in males only during the 104-week oncogenicity study of rats

Non-neoplastic finding in male rats		Dosage levels (mg/kg/day)				
		Controls		low	mid	high
		0	0	180	600	2000
Mineralization of pelvic/papillary transition epithelium	total	26	19	25	26	39**
	trace	4	5	15*	12	7
	minimal	20	13	9	14	30**
	moderate	2	1	1	0	2
Dilated suburothelial capillaries		0	1	0	2	7*
Total number of rats examined		55	55	55	55	55

* = p <0.05, ** = p <0.01, one-sided, Fischer's Exact Test, combined controls compared with low, mid and high dose groups.

Table 16
Non-neoplastic findings in females only during the 104-week oncogenicity study of rats

Non-neoplastic finding in female rats		Dosage levels (mg/kg/day)				
		Controls		low	mid	high
		0	0	300	1000	3000
Mineralization of pelvic/papillary transition epithelium	total	47	43	45	51*	51*
	trace	6	5	3	7	7
	minimal	38	35	39	42	38
	moderate	3	3	3	2	5
Total number of rats examined		55	55	55	55	55

Fisher's Exact Test, combined controls compared with low, mid and high dose groups.

* = p <0.05
** = p <0.01, one sided

Comments: The potential oncogenicity of lamivudine was investigated in rats at dosages of 180♂/300♀, 600♂/1000♀ or 2000♂/3000♀ mg/kg/day in comparison with untreated controls for a period of 104 weeks. The study protocol was approved by the ECAC.

Histopathological examination showed a slight increase in the incidence of endometrial epithelial tumors in female rats (high).

The incidence was only slightly higher (5/55 or 11%) than historical control values (4/50 or 8%) but did not achieve statistical significance in a trend test in this study. There was no increase in incidence of pre-neoplastic findings in the endometrium (for example proliferative changes) in the dosed groups. There was no statistically significantly increased incidence of any proliferative non-neoplastic epithelial lesions in treated female rats when compared to the controls.

The only non-neoplastic finding of note was an increased incidence and severity of mineralization in the kidney (mid and high) with accompanying suburothelial capillary dilatation in male rats (high). This was considered an exacerbation of a normal age-related change commonly seen in rat kidney.

Lamivudine was not oncogenic in rats. For oncogenic potential, a dosage of 2000♂/3000♀ mg/kg/day was the NOEL. For a clinical dose of 150 mg bid, the average steady state systemic exposure (AUC) and peak plasma concentration (Cmax) values were 7.8 µg*hr/ml and 1.9 µg/ml, respectively. The average systemic AUC measured at the dose level of 2000♂/3000♀ mg/kg/day during week 5 of the study wa 533♂/880♀ µg*hr/ml. Based on the average AUC in the clinic, the high dose in the rat study represented 68- to 113-fold overdosages; thus, an equivalent dose in humans would be 10.2♂/16.9♀ g bid.

3. Lamivudine: mammalian cell mutation test at the thymidine kinase locus in mouse lymphoma L51178Y cells (T21234), Lot # UFP1027/1, [redacted] 2 February 1996, (WPT/96/029)

In an in vitro mammalian cell mutation assay, lamivudine (concentrations: 500, 1000, 1250, 2500, 3750 or 5000 µg/ml) was tested at the TK locus of mouse lymphoma L5178Y cells (T21234) in the absence of S9-mix for a period of 3 hr (ICH recommendations). Results: lamivudine treatment caused a little cytotoxicity over the 3 hr treatment period. The relative survival was reduced to 89% (5000 µg/ml). A similar reduction was observed at all lower concentrations. No statistically significant increases in mutant frequency were seen at any of the concentrations tested. Conclusion: lamivudine was not mutagenic in the mouse lymphoma test system after a 3 hr treatment in the absence of S9-mix.

4. Lamivudine: lack of activity in a bone marrow micronucleus test following oral administration to male Han Wistar rats. Lot # UFP1027/1, [redacted] June 1996, (WPT/96/028)

Groups of male AHA rats (7/group) were orally gavaged lamivudine at dose levels of 0 or 2000 mg/kg/day for 3 days. Approximately 24 hr after the final dose, all rats were killed by cervical

dislocation. Marrow was aspirated from the femurs of all rats and smears were prepared. The smears were subsequently fixed, stained and analyzed for the incidence of MPCE (clastogenic potential) and the ratio of polychromatic to normochromatic erythrocytes (cytotoxic or cytostatic potential). Results: there was no increase in MPCE when compared with the controls. There was no statistically significant decrease in the proportion of PCE to NCE in the lamivudine treatment group when compared with the controls. Conclusion: lamivudine was not clastogenic in an in vivo micronucleus assay. There was no cytotoxic or cytostatic effect on erythroblast proliferation.

Comments: Long-term administration of Lamivudine in mice and rats provided no evidence of carcinogenic potential. These findings were presented to the Exec CAC for evaluation and concurrence. The committee concurred with the adequacy of the study and the non oncogenic potential of the compound. Subsequently, the results were incorporated in a revision to the current FDA-approved labeling for Epivir Tablets and Epivir Oral solution.

5. Lamivudine: supplementary report to 13-week oral toxicity study of lamivudine in dogs, Glaxo Ltd, Hertfordshire, England, 17 October 1994, (VTX/94/037)

This report contains supplementary information to Report number WPT/92/132 which described the finding of a 13-week oral toxicity study of lamivudine in dogs. The microscopic examination of the caecum, which was not included in the original protocol design, was performed on all dogs following the detection of caecal changes in the 6-month rat study (WPT/93/361). This supplementary report has been submitted to include the results of this examination. The caecum was fixed in 10% neutral buffered formalin (WPT/92/132). Results: no microscopic changes related to lamivudine administration were observed in the caecum of any animals killed either at the end of the treatment or recovery periods.

6. Summary report of lamivudine: pericardial effusion as an artifact in the AHA rat foetus, Glaxo Ltd, Hertfordshire, England, 12 July 1995, (WPT/95/213)

In an preliminary rat organogenesis study using the racemate [redacted] (Study # WPT/90/106), an increased incidence of unusually dark colored pericardial effusion was recorded only in fetuses from treated animals. This observation was investigated in a further two studies using lamivudine and in an experiment designed to clarify the circumstances in which the observation may be induced. This report presents a review of the findings relating to the occurrence of pericardial effusion in these studies. Maternal data were not presented in this report. Summary of results: this report suggests that the cause of the

pericardial effusion recorded in the AHA rat fetuses was due to an artifact (ie, in unusually large fetuses delays in penetration of the fixative was associated with dark coloration of pericardial effusions).

LABEL AND LABELING:

Carcinogenicity, Mutagenesis, Impairment of Fertility, and Pregnancy: The sponsor has modified the Label to incorporate results of the 2-year carcinogenicity studies in mice and rats. The changes are acceptable.

CONCLUSIONS:

NOELs from the 6-month rat and 12-month dog toxicology studies were compared with the human therapeutic dose of 100 mg once daily [approx. 2.0 mg/kg/day; AUC = 4.4 μg*kg/ml]. For instance, in the 6-month rat and 12-month dog toxicity studies, the NOELs were 850 mg/kg/day (AUC = 132 μg*hr/ml) and 90 mg/kg/day (AUC = 74.5 μg*hr/ml), respectively. On the basis of the drug exposure comparisons from the rat and dog NOELs, equivalent doses in humans would be 27.3 mg/kg/day and 16.9 mg/kg/day, respectively. Based on the body surface area conversion factor, the equivalent doses in humans as calculated from the rat and dog study NOELs would be 138 mg/kg/day and 48.6 mg/kg/day, respectively. Thus, based on both body surface area or pharmacokinetic principles, the exposure to humans at the clinical dose of 100 mg once daily (approximately 2 mg/kg/day) is substantially lower than that seen in the animal studies at the NOELS.

There are no nonclinical pharmacology and toxicology issues which would preclude the approval of this NDA.

/S/

Pritam S. Verma, Ph.D.
Reviewing Pharmacologist

Concurrences:

HFD-530/WDempsey AD 8/25/98
HFD-530/JFarrelly JD 7/22/98
HFD-530/PVerma PSV 7/22/98

Disk:
HFD-530/JFarrelly

cc

HFD-530/NDA 21-003
HFD 340
HFD-530/PVerma
HFD-530/BStyrt
HFD-530/GLunn
HFD-530/LConnors
HFD-530/AZeccola

APPENDIX # 1:

The Summary of Toxicology and Pharmacokinetics Sections of NDAs 20-564 and 20-596.

Acute toxicity studies: lamivudine has a low acute toxicity via the oral or iv routes in both mice and rats. The acute oral or iv administration of lamivudine (4000 mg/kg) was adequately tolerated by both mice and rats and was not associated with any target organ toxicity.

Chronic toxicity studies: lamivudine was adequately tolerated in the rat at doses up to 2000 mg/kg/bid for 6 months. Treatment-related effects included minor hematological (mainly red blood cell parameters), clinical chemistry and urinalysis changes, and mucosal hyperplasia of the caecum. A dose of 450 mg/kg/day was identified as a NOEL. Based on the drug exposure comparisons, a dose of 16.9 mg/kg/day would be considered an equivalent dose in humans. In dogs, doses of 1500/kg/bid in males and 1000 mg/kg/bid in females for a period of 12 months were adequately tolerated. Treatment-related changes included reductions in red cell counts at all dose levels, associated with increased MCV and MCH, and reductions in total leucocyte, neutrophil and lymphocyte counts in high dose animals, but with no effect on bone marrow cytology. A dose of 45 mg/kg/day was identified as a NOEL. Based on the drug exposure comparisons, a dose of 9.5 mg/kg/day would be considered an equivalent dose in humans.

ADME studies in rat, dog and man: following iv administration to the rat, lamivudine showed a bi-exponential elimination with

dominant half-life of about 20 min. Lamivudine was cleared almost entirely by renal elimination in rats. The value for renal clearance (3.3 ml/min) exceeded the GFR in rats and thus tubular secretion must play a significant role in the elimination of lamivudine in this species. Lamivudine was rapidly and extensively absorbed following an oral administration as evidenced by a Tmax of about 1 hr and oral bioavailability of about 60% in the rat and 80% in the dog. The oral bioavailability of lamivudine in man was approximately 80%. Data from studies with radiolabelled lamivudine in dog following an oral or iv administration showed that lamivudine accounted for 40% of the plasma radiolabelled drug due to the presence of circulating metabolites. Following an oral administration to the dog, approximately 97% of a radiolabelled dose of lamivudine was recovered in the urine. The bioavailability of lamivudine in the dog was limited by metabolism rather than absorption. This was in contrast to the rat where about 35% of an oral dose was recovered in feces as unchanged lamivudine suggesting that in this species the bioavailability was limited by incomplete absorption.

Following the oral or iv administration of radiolabelled lamivudine to the rat, the majority of the radiolabelled drug was excreted in the urine. Thus, approximately 90% of the iv dose and 60% of the oral dose was excreted in the urine in the first 24 hr. The unchanged drug accounted for up to 96% of the urinary excreted radioactivity for both the routes of administration. Urinary excretion was also predominant following the oral or iv administration of lamivudine to dogs, with up to 99% of a radiolabelled dose excreted in the urine in the first 24 hr. In contrast to the rat, metabolic clearance played a significant role in the clearance of lamivudine in the dog.

Studies performed in man showed that the renal clearance of unchanged drug was the predominant mechanism of clearance for lamivudine. Approximately 85% of an iv dose and 70% of an oral dose was excreted as unchanged drug in the urine. The trans-sulfoxide metabolite of lamivudine was identified in urine samples from patients following the repeated oral administration, accounting for about 5% of the administered dose. Lamivudine did not undergo extensive first-pass metabolism. The absolute bioavailability of the compound is likely to be same as the amount absorbed. Thus, about 90% of the orally absorbed drug was accounted for in the urine as either parent or the trans-sulfoxide of lamivudine. The remaining portion of the oral dose was likely to be material unabsorbed from the gastrointestinal tract. In conclusion, the excretion and metabolic profile of lamivudine in man was more like that seen in the rat than in dog.